Original Article

Hemodynamic effects of low-dose bupivacaine spinal anesthesia for cesarean section: A randomized controlled trial

ABSTRACT

Background: Spinal anesthesia is the most common technique for cesarean section. The conventional local anesthetic dose has been decreasing over time to 8–12.5 mg of bupivacaine. Lower doses of bupivacaine may be associated with reduced incidence of hypotension and other complications. This low dose also may be associated with improved maternal cardiac index (CI). We hypothesized that low dose spinal anesthesia using 4.5 mg bupivacaine would result in improved maternal CI when compared with conventional dose (9 mg) intrathecal bupivacaine.

Methods: This randomized controlled trial included all healthy parturients presenting for elective cesarean section. In addition to standard monitors, an arterial line was placed for pulse contour cardiac output measurement. Due to limited data on maternal cardiac output during cesarean section, we had to power our study on recovery room length of stay. Secondary outcomes included the change in maternal CI, fluid administration, vasopressor usage, maternal satisfaction, and adequacy of surgical blockade and recovery time from motor and sensory blockade.

Results: The low dose group had significantly faster motor recovery times (132 [122–144] versus. 54 [48–66] min conventional versus. low-dose, respectively, $P < 0.01$), and a shorter recovery room stay (92 ± 21 vs 70 ± 11 min, conventional vs. low-dose, respectively, $P < 0.01$, 95% CI -35 to -10 min). There was no difference in CI between the conventional dose and low dose spinal groups. Both groups had a drop in CI with spinal anesthesia. The low-dose group demonstrated equivalent surgical anesthesia and block onset times compared to the conventional group.

Conclusions: Low-dose spinal anesthesia provides adequate surgical anesthesia, improved recovery time, but no difference in maternal cardiac index when compared to conventional dose spinal anesthesia.

NCT02046697

Key words: Cardiac output; cesarean section; hemodynamics; obstetric anesthesia; spinal anesthesia

Introduction

The incidence of hypotension during spinal anesthesia for cesarean section can be as high as 70–80% with conventional local anesthetic doses.[1,2] Despite attempts at preventing inferior vena cava compression through left lateral tilt

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and volume loading with crystalloid and colloid infusions, hypotension remains a persistent complication of spinal anesthesia.[3] Aside from the negative impact of hypotension on the mother and the fetus, vasopressor use to correct hypotension has been associated with abnormal acid base status in neonates.[4]

Studies looking at combined epidural with low-dose spinal (3.75–7 mg of hyperbaric bupivacaine) anesthesia showed a lower incidence of hypotension and faster recovery from sensory and motor blockade without compromising adequacy of surgical analgesia.[5-8] The lower bupivacaine dose is also thought to contribute to less nausea and less vasopressor use.[6,9] Previous work has shown that neonatal outcomes as assessed by Apgar scores or acid-base status are not different between low and conventional dose spinals; however, most studies are underpowered to be able to show a significant difference.[4]

The studies to date compared low dose and conventional dose combined spinal-epidurals or they compare low dose plus narcotic to conventional spinals without narcotic.[10] The present research study is different in that it compared low dose to conventional dose hyperbaric bupivacaine spinal anesthesia with equivalent doses of intrathecal narcotic in each group. In addition, patient position was manipulated in an attempt to adjust block height as well as improve venous return and hemodynamics.

We hypothesized that low-dose spinal anesthesia would result in improved maternal cardiac index (CI). Due to limited data on the cardiac output of parturients undergoing cesarean section, we were not able to determine a sample size for this study based on this parameter (which would have been ideal). We therefore powered our study, and therefore used as a primary outcome, recovery room length of stay. As such, this study is exploratory in nature with respect to maternal hemodynamics and can be used in future studies for sample size planning.

Methods

This trial is registered at Clinicaltrials.gov as NCT02036697 and was approved by the [BLINDED]. Written informed consent was obtained from all patients.

Patients were included in the study if they were over the age of 18 and presenting for an elective cesarean section at the [BLINDED]. Exclusion criteria included any patients with a contraindication to dural puncture, body mass index (BMI) >40, patients presenting in labor or with rupture of membranes and any patients scheduled for cesarean section due to abnormal placentation. Randomization occurred via sealed envelopes that were created prior to study commencement utilizing a 1:1 allocation ratio. The patient and obstetrician were blinded to group allocation, the treating anesthesiologist was not.

All patients had standard Canadian Anesthesia Society monitors placed. In addition, a radial arterial catheter was inserted prior to administration of the spinal for continuous blood pressure and cardiac output measurements using the FloTrac cardiac output monitor (Edwards LifeSciences, Irvine, CA, USA).

The conventional dose control group received spinal anesthesia consisting of 9 mg of 0.75% hyperbaric bupivacaine with 15 mcg of fentanyl and 150 mcg of preservative free morphine. The spinal was placed with patients in the sitting position. They were then positioned supine in left lateral tilt for the duration of the cesarean section.

The low-dose spinal group received spinal anesthesia consisting of 4.5 mg of 0.75% hyperbaric bupivacaine with 15 mcg of fentanyl and 150 mcg of preservative free morphine. These patients had their spinal anesthetic administered in the right lateral decubitus position with 10° trendelenburg position. The head down position was used to direct the hyperbaric solution preferentially to achieve a T-6 level of anesthesia. They were then positioned supine with left lateral tilt and kept in the 10° trendelenburg position for the duration of the cesarean section.

Heart rate (HR), mean arterial pressure (MAP), stroke volume index (SVI), and CI were monitored continuously. The treating anesthesiologist was blinded to the CI measurements.

A patient controlled analgesia (PCA) infusion of remifentanil was set up for all patients and they were trained how to administer PCA boluses if they suffered any discomfort during the case. Total remifentanil dose was used as a measure of adequacy of pain control in each group. If adequate analgesia was not obtained, 60–70% nitrous oxide was administered via facemask. If despite remifentanil PCA and nitrous oxide administration analgesia were inadequate, conversion to general anesthesia would be performed. Rectal naproxen was administered at the conclusion of surgery. Ondansetron was administered at delivery for postoperative nausea and vomiting prophylaxis.

Hypotension, defined as a decrease in MAP to less than 80% of the baseline noninvasive blood pressure, was treated

with incremental doses of phenylephrine (50-100 mcg IV), or ephedrine (5 mg IV) if maternal HR was less than 60 beats per minute. A 500 cc Ringer's Lactate bolus was administered when the MAP decreased to 90% of baseline following the spinal anesthetic. Additional fluids were administered as clinically indicated and the total dose of intravenous fluids was recorded.

Standard infusions of oxytocin 20 U in 500 mL normal saline were started with delivery of the baby. Additional uterotonics were given as clinically indicated.

Levels of sensory and motor blockade ware recorded immediately postrepositioning to the left lateral tilt position, then every 5 min until levels were at T6 to ensure adequate analgesia for skin incision. Sensory blockade was assessed using ice and motor block was assessed using the modified Bromage score. Sensory and motor block were assessed on arrival to recovery room and then every 15 min until sensory levels regressed below T10. Patients were deemed fit for discharge if they met usual discharge criteria at our institution, which is an Aldrete score of >8 and a Bromage score of >4.

Arterial and venous umbilical cord blood gases were obtained in both groups at the time of delivery.

Maternal satisfaction of pain relief, nausea/vomiting, shivering, and ability to interact with the baby was assessed via a nonvalidated questionnaire in the recovery room. Obstetrician satisfaction with adequacy of analgesia as well as muscle relaxation was assessed via a nonvalidated questionnaire following the cesarean section.

Due to a lack of published data on the effect of spinal dose on maternal CI we powered our study based on recovery room length of stay. The primary outcome was the recovery room length of stay. Our secondary outcome was the change in CI over time from the start of the spinal anesthetic to 15 min after its placement. We chose this time period as this was presumed to be the most hemodynamically volatile time period that could be attributed to the spinal anesthetic.

Other parameters measured included:

1. Surgical time (skin incision to skin closure)
2. Total dose of remifentanil administered during the case.
3. Total phenylephrine and ephedrine administered during the case
4. Fetal cord blood gases (arterial and venous) at delivery
5. 1 and 5 min Apgar scores
6. Maternal satisfaction scores
7. Obstetrician satisfaction scores.

Our research technician and a senior anesthesiology resident in our department conducted the study. The treating clinician and our research staff were not blinded to treatment allocation. The hemodynamic and outcome data were analyzed by the senior authors (S.K., D.M., and D.F.) who were blinded to patient allocation.

Statistical analysis

Trial results were analyzed on an intention to treat basis.

Demographic data is represented as mean (SD) for normally distributed data, or median [interquartile range] for nonnormally distributed data. Normality was tested with the D'Agostino and Pearson omnibus normality test. Between group continuous variables were analyzed with a Student's *t*-test for normally distributed data and with a Mann–Whitney test for nonnormally distributed data. When comparing the hemodynamic data between groups, we looked at the first 15 min of the case and compared these values with two-way repeated measures analysis of variance (ANOVA).

All results were considered statistically significant if $P < 0.05$. Analysis was performed using GraphPad Prism Software (Version 6.0d for Mac, San Diego, CA, USA).

The primary endpoint was the expected reduction in the recovery room length of stay. Based on a predicted 50% reduction in length of stay, alpha 0.05, power of 80%, and an anticipated drop-out rate of 10%, we calculated a sample size a sample size of $n = 20$ patients per group.

Results

Patients were recruited between September 2013 and June 2014. Of 143 patients reviewed, 31 did not meet inclusion criteria, 77 declined to participate, and 3 who consented to participation delivered prior to their scheduled cesarean section [Figure 1].

The trial was terminated early due to slow enrollment after 30 patients. Thirty-two patients were randomized. Two patients in the conventional dose group withdrew their participation prior to any intervention. All remaining patients, 16 in the low dose spinal group and 14 in the conventional spinal group were followed up to completion.

Patient demographic data are presented in Table 1. Patients in the conventional dose spinal and low dose spinal group were

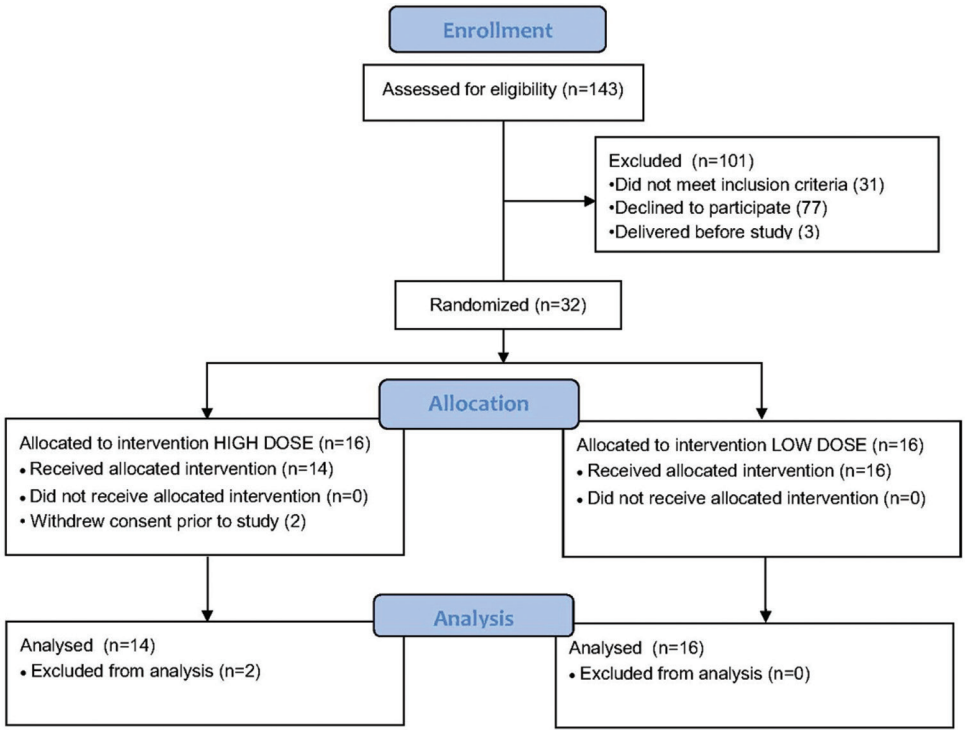

Figure 1: Consort Flow Diagram

well matched at baseline. The average age in the conventional dose group was 31 ± 3 versus 32 ± 6 years in the low dose group. BMI was similar between groups, 30.6 ± 5.4 kg•M^2 in the conventional dose group and 31.0 ± 4.0 kg•M^2 in the low dose group. Similarly, gestational age was similar between groups (39.1 ± 0.5 vs. 39.1 ± 0.7 weeks, conventional dose vs. low dose, respectively).

Intraoperative characteristics are presented in Table 2. Surgical time was similar between groups. Intravenous fluid administration was slightly higher in the conventional dose spinal group (1457 ± 447 vs. 1247 ± 338 mL, conventional vs. low-dose, respectively, $P = 0.15$). The total dose of phenylephrine administered was higher in the conventional dose group, but this failed to reach statistical significance (407 ± 341 vs. 300 ± 226 mcg, conventional vs. low dose, respectively, $P = 0.31$). Three patients in the high-dose group and one in the low-dose group received ephedrine. Estimated blood loss was significantly higher in the conventional dose group when compared to the low dose group (657 ± 116 vs. 569 ± 108 mL, $P = 0.04$).

Time spent before discharge from the recovery room was significantly higher in the conventional vs. low-dose group [92 ± 21 vs. 70 ± 11 min, conventional vs. low dose respectively, $P < 0.01$, 95% CI -35 to -10 min, see Figure 2]. There were also significant differences in the time to motor recovery with patients in the conventional dose spinal group achieving this milestone at 132 [122–144] min compared with 54 [48–66] min in the low-dose group [Figure 2, $P < 0.01$]. Surgical time was not significantly different between groups (50 ± 10 min vs. 48 ± 12 min, conventional vs. low dose, respectively,

Table 1: Baseline Demographics

	High dose	Low dose
Age (years)	31.3±3.3	32.6±6.0
BMI kg•M^2	30.6±5.4	31.0±4.0
Gestational age (weeks)	39.1±0.5	39.1±0.7

Values are mean±SD. BMI: Body mass index

Table 2: Intraoperative data

	High dose	Low dose	*P*
Surgical time (min)	50±10	48±12	0.75
Fluid administration (mL)	1457±447	1247±338	0.15
Phenylephrine dose (mcg)	407±341	300±226	0.31
Estimated Blood loss (ml)	657±116	569±108	0.04
Time to motor recovery (min)	132 [122-144]	54 [48-66]	<0.0001
Time to sensory recovery (min)	153 [71-180]	103 [69-136]	<0.0001
Discharge from recovery room (min)	92±21	70±11	<0.0001
Apgar			
1 min	8 [8-9]	9 [8-9]	0.24
5 min	9 [9-9]	9[9-9]	0.48
Umbilical vein pH	7.25±0.04	7.26±0.02	0.55
Remifentanil use (number of patients)	2	2	NS

Data are represented as mean±SD for normally distributed data or median (interquartile range) for non-normally distributed data. Mcg: Micrograms

P = ns). Time to onset of block to T6 was similar in the conventional dose versus low-dose groups (4.3 ± 1.7 vs. 3.4 ± 1.2 min, respectively).

When comparing baseline hemodynamics (CI, MAP, SVI, HR), there were no differences between the conventional dose and low-dose spinal groups [Table 3].

CI dropped significantly in both groups from the start of the case to the 15-min time period [Figure 3, $P < 0.0001$, two way repeated measures ANOVA]. The decrease in CI however was not significantly different between groups ($P = 0.36$, group vs. time interaction). With respect to MAP, there was a positive group vs. time effect with patients in the conventional dose spinal group having higher MAPs than the patients in the low-dose spinal group [Figure 4, $P < 0.001$, group vs. time effect]. This was possible due to the higher dose of phenylephrine that these patients received.

There were no differences between groups in 1- or 5-min Apgar scores, or in umbilical artery or venous pH [Table 2]. We then compared the drop in CI and neonatal venous pH. There was no correlation between the neonatal venous pH and the absolute drop in CI in the low-dose spinal group, but there was in the conventional dose spinal group, with larger decreases in CI being correlated with lower umbilical venous pH [Figure 5, $r^2 = 0.44$].

There was no correlation between administered phenylephrine dose and the drop in CI in either group.

Two patients in each group used the remifentanil PCA for breakthrough pain. The average pain score on a 10-point scale was 1.2 in the conventional dose group versus 1.1 in the low dose group. Average maternal satisfaction score on a 10-point scale was 9.6 in the conventional dose group versus 9.1 in the low-dose group. The incidence of perioperative nausea and vomiting was similar between groups (8/14 vs. 6/16, conventional dose vs. low dose respectively, $P = 0.46$, Fisher's exact test).

Obstetrician satisfaction with the block was also similar on a 10-point scale (8.7 low dose versus 7.8 conventional dose). When obstetricians were asked what type of block the patient had, they guessed correctly less than 50% of the time.

Discussion

Our study, not surprisingly, showed that women given a conventional dose spinal anesthetic (9 mg bupivacaine) had a longer recovery room time than women given a low dose (4.5 bupivacaine) spinal anesthetic.

Our study did not demonstrate any difference in CI between conventional or low-dose spinal anesthesia. This lower dose did not compromise surgical conditions or patient satisfaction. In addition, patients in the low dose group

Table 3: Baseline hemodynamic data

	High dose	Low dose
CI (l•min^{-1}•M^2)	4.8±0.6	4.6±0.6
SBP (mmHg)	148±22	135±11
MAP (mmHg)	97±11	97±10
SVI (mL•M^2)	54±7	55±11
HR (bpm)	88±6	83±11

Data are mean±SD. CO: Cardiac output, CI: Cardiac index, SBP: Systolic blood pressure, MAP: Mean arterial pressure, SVI: Stroke volume index, HR: Heart rate, bpm: Beats per minute

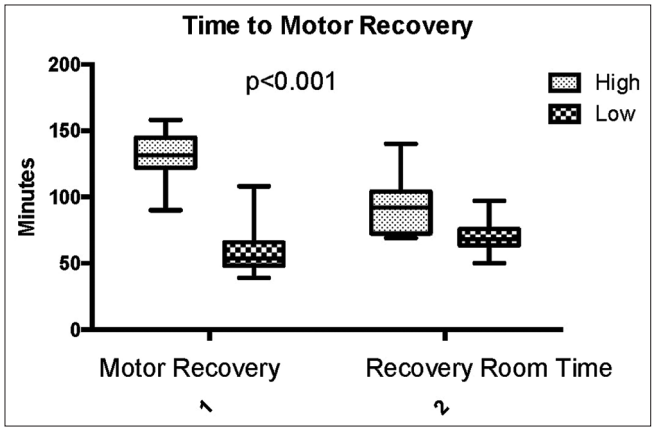

Figure 2: Difference in motor recovery and discharge from recovery room time. There were significant differences in the time to motor recovery (132 [122–144] vs. 54 [48–66] min conventional dose vs. low-dose group, respectively, $P < 0.01$). Time spent before discharge from the recovery room was also shorter in the low-dose group (92 ± 21 vs. 70 ± 11 min, conventional dose vs. low-dose group, respectively, $P < 0.01$)

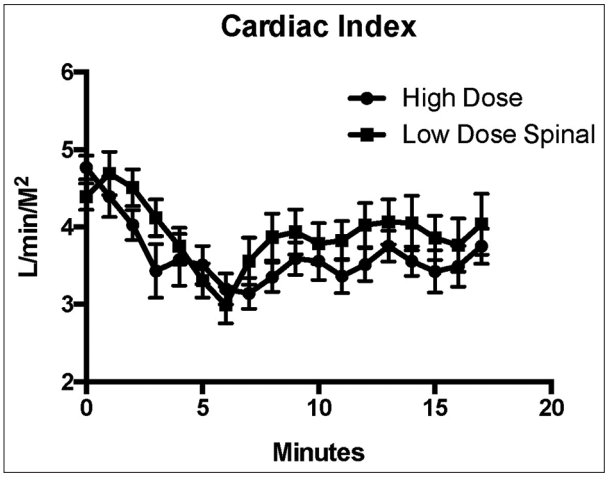

Figure 3: CI after spinal anesthesia. CI dropped significantly in both groups from the start of the case to the 15-min time period ($P < 0.0001$, two-way repeated measures ANOVA). The decrease in CI was not significantly different between groups ($P = 0.36$, group vs. time interaction)

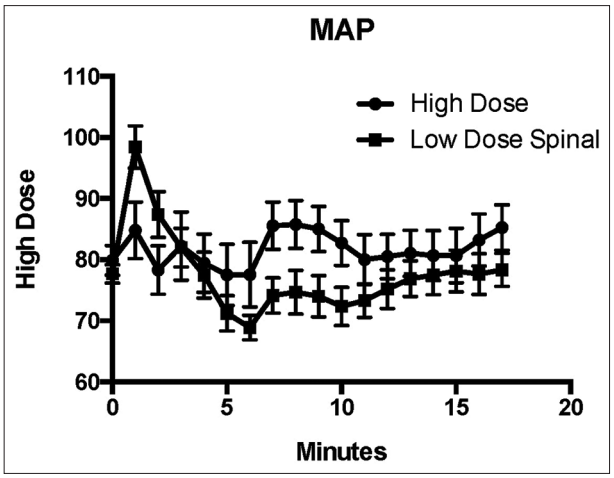

Figure 4: MAP after spinal anesthesia. There was a positive group versus time effect with patients in the conventional dose spinal group having higher MAPs than the patients in the low-dose spinal group (Figure 3, $P < 0.001$, group vs. time effect)

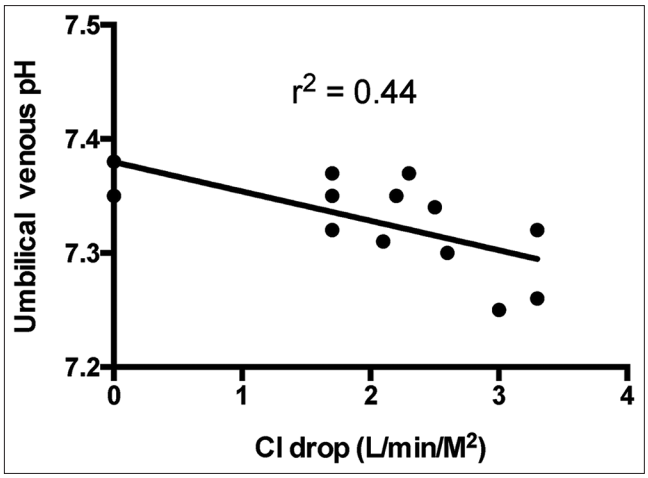

Figure 5: Change in umbilical vein pH as a function of decrease in CI, conventional dose spinal group. There was no correlation between the neonatal venous pH and the absolute drop in CI in the low-dose spinal group, but in the conventional dose spinal group larger decreases in CI were correlated with lower umbilical venous pH ($r^2 = 0.44$)

recovered motor function and sensory levels faster and had shorter recovery room stays.

Despite higher (but nonsignificant) phenylephrine and fluid requirements in the conventional dose group, we did not demonstrate any difference in the magnitude of hypotension between groups. This is in contrast to previous studies that showed improved hemodynamic stability in the low dose spinal groups.[5-8] The difference between these studies and our work may be the result of a smaller sample size in our study. In addition, our study was different in that the low dose group was positioned in 10° trendelenburg, while the conventional dose group was not. It is possible that this contributed to a higher sympathetic blockade and caused hemodynamic changes similar to the conventional dose group.

A novel finding of our study was that in the conventional dose spinal group, there was a moderate correlation between the absolute drop in CI and neonatal pH [Figure 5]. Previous work has suggested that flow through the dilated vascular bed of the uterus is largely pressure dependent and does not correlate with flow.[11] Our finding of a correlation between absolute drop in CI and umbilical vein pH suggests that there may exist a threshold CI below which fetal oxygen delivery is compromised. Typically, uterine blood flow exceeds minimal fetal requirements and provides it with a margin of safety.[12,13] Once this margin is exceeded; however, fetal acidosis may result. This finding occurred despite a preserved MAP, suggesting that, as in other organ beds, pressure does not equate to flow.[14,15]

A similar study conducted by Langesaeter *et al.* showed an increase in CI with the use of varying dose spinal anesthesia and phenylephrine administration in women undergoing cesarean section.[16] Our study did not demonstrate an increase in CI in the first 15 min after spinal anesthesia. In both of our study groups, there was a statistically significant drop in CI from baseline likely reflecting the decrease in venous return caused by the sympathectomy in each group.

A recent study in parturients, using MRI imaging, demonstrated that there was significant compression of the inferior vena cava in the supine and 15° left lateral tilt position and it was only when the tilt was increased to 30° that compression of the inferior vena cava was relieved.[17] The patients in this study all had left lateral tilt of 10° to 15° and it is therefore possible that this amount of lateral tilt decreased CI to a greater degree than was seen in the Langesaeter study. That study did not comment on their degree of uterine tilt.

It is also possible that the differences in CO monitors used between our study and that of Langesaeter could explain the differences seen in CI response. The pulse contour systems (LiDCO and Vigileo) that were utilized for both studies have shown difficulty in tracking changes in CI.[18-20] We used the latest software version for the FloTrac system, which has shown improved accuracy in measuring CI in patients with varying systemic vascular resistance.

The low-dose spinals demonstrated comparable block onset times, maternal and obstetrician satisfaction scores, and surgical conditions. The ability of obstetricians to distinguish these blocks from conventional spinals was equivalent to random chance. The patients, however, benefited from shorter stays in recovery room, faster mobilization, and fewer interventions through sensory and motor checks in the recovery room.

All 30 patients in our study had adequate analgesia to complete the cesarean section without conversion to general anesthesia. In the two patients in each group who used the remifentanil PCA, the PCA was initiated near the time of delivery of the baby rather than at the end of the case demonstrating that block duration for these cesarean sections was adequate.

There are several limitations to our study that must be addressed. First this is a small, single center study that failed to meet its target enrollment due to slow patient recruitment. As such, it was not powered to reach conclusions for its primary nor secondary outcomes. Second, as with all minimally invasive cardiac output monitors, there is error in CO measurement that may be as high as 20%, and a true difference may have been present between groups that were not detected. Finally, patient position for the administration of the spinal, and the subsequent position differences may have negated any CI difference between groups. We chose to place the low-dose patients in trendelenburg position in order to ensure adequate block height in order to ensure adequate surgical anesthesia. This may have caused a similar decrease in CI as was seen with the conventional dose group, with subsequent vasodilation of the splanchnic bed leading to decreased venous return and CI.[14,15,21]

In conclusion, low-dose intrathecal bupivicaine for cesarean section demonstrated equivalent changes in CI when compared to conventional dose bupivicaine. The low-dose bupivicaine group did however benefit from a more rapid recovery of sensory and motor blockade, faster discharge from recovery room and equivalent patient satisfaction to conventional dose bupivicaine. The absolute drop in CI in the conventional dose bupivicaine group was correlated with decreases in umbilical venous pH.

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University of Manitoba Department of Anesthesia Academic Oversight Committee.

Conflicts of interest

There are no conflicts of interest.

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